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Comparative Effects of Na^+/H^+ Exchange Inhibitors Against Cardiac Injury Produced by Ischemia/Reperfusion, Hypoxia/Reoxygenation, and the Calcium Paradox

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Summary: To examine the role of Na^+/H^+ exchange in cardiac injury, we compared the effect of amiloride (174 μM) with the markedly more specific and potent inhibitor 5-(*N*,*N*-hexamethylene) amiloride (HMA, 1 μM) against cardiac injury produced by reperfusion, reoxygenation, and the calcium paradox. Reperfusion after 15-min ischemia resulted in a 55 ± 4% recovery in contractility, whereas in the presence of amiloride or HMA, recovery was increased to 82 ± 5.8 and 72 ± 7.8%, respectively ($p < 0.05$ from control), with HMA showing particular efficacy in accelerating recovery. The rapid restoration of function with HMA was also evident in hearts reoxygenated for 1 min after 12-min hypoxia (control 35 ± 3.2%, HMA 66 ± 4.1%, $p < 0.05$) although the protective effect gradually reversed with continued reoxygenation. On the other hand, with addition of amiloride, the protective effect persisted so that after 30-min reoxygenation values were significantly higher than control (65 ± 4.1 vs. 47 ± 3.1%, $p < 0.05$). Resting tension increases after either reperfusion or reoxygenation were moderate: 124 ± 8 and 119 ± 6%, respectively ($p > 0.05$), but no increases were observed with amiloride or HMA. Bepridil (10 μM), a purported Na^+/Ca^{2+} exchange inhibitor, exerted a salutary effect against reperfusion dysfunction identical to that of amiloride and HMA, whereas in reoxygenated hearts the effects were identical to those observed with HMA. The protective effects of the drugs were not related to improved energy metabolic status. None of the pharmacologic interventions exerted beneficial effects against the calcium paradox. The present results support the concept of Na^+/H^+ exchange-mediated injury, possibly linked to Na^+/Ca^{2+} exchange activation, in reperfused and reoxygenated myocardium but not in hearts subjected to the calcium paradox. Key Words: Heart—Amiloride—Hexamethylene amiloride—Contractility—Energy metabolism—Na^+/Ca^{2+} exchange—Oxygen paradox.

Reperfusion of the ischemic myocardium produces substantial tissue injury (1,2). The mechanisms underlying such injury are not well understood, although extensive evidence shows that it occurs as a consequence of numerous intracellular processes (1,2). We previously showed that amiloride can reduce such injury, possibly by preventing activation of Na^+/H^+ exchange at the time of reflow (3). Our study was based on the suggestion that Na^+/H^+ exchange is rapidly activated at the time of reperfusion owing to the initial ischemia-induced intracellular acidosis and the subsequent attempt to restore intracellular pH after return of flow by extruding protons against the inward-directed Na^+ gradient through Na^+/H^+ exchange (4). Paradoxically, this process can result in various deleterious events such as increases in intracellular calcium through Na^+/Ca^{2+} exchange or, as demonstrated in platelets, stimulation of phospholipase A_2 leading to phospholipid breakdown and subsequent membrane damage (4,5).

A potential mechanism for implication of Na^+/H^+ activation in reperfusion injury is the large accumulation of intracellular lactate caused by anaerobic metabolism, resulting in an acid load (6,7). Indeed, this readily occurs during ischemia owing to poor washout of the glycolytic product (7). Various other models of tissue injury have been developed

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to investigate the mechanisms of myocardial ischemic and reperfusion injury. The "oxygen paradox" results in marked tissue injury when oxygen is reintroduced after a period of normal-flow hypoxia (8). The "calcium paradox" represents a widely studied model of uncontrolled cellular calcium entry that occurs when calcium is reintroduced after a brief period of calcium-free perfusion (8). Although similarities between these pathologic models have been suggested (8), each may possess distinct underlying mechanisms and different modes of tissue protection against the three forms of insult may exist. Because of the emerging importance of Na^+/H^+ exchange in mediating tissue damage, we compared the efficacy of pharmacologic agents reported to inhibit Na^+/H^+ exchange with respect to their salutary actions against injury produced by ischemia and reperfusion as well as the oxygen and calcium paradox. We reemphasize that the deleterious effect of Na^+/H^+ exchange activation can in large part be attributed to subsequent Na^+/Ca^{2+} stimulation, resulting in increased intracellular calcium levels. To assess this indirectly, we also examined the effects of bepridil, a purported Na^+/Ca^{2+} exchange inhibitor (9) on tissue injury produced by the three modes of insult.

METHODS

Animals

Male Sprague-Dawley rats weighing 250–300 g were obtained from Charles River Canada (St. Constant, Quebec, Canada). Animals were housed in the animal care facilities at the University of Western Ontario in accordance with guidelines provided by the Canadian Council on Animal Care (Ottawa, Ontario, Canada).

Heart perfusion

For heart perfusion, rats were killed by decapitation and the hearts were rapidly excised and placed in ice-cold Krebs-Henseleit buffer, which produced immediate cessation of contraction. The heart was squeezed a few times with fingers to dislodge any clotted blood in the coronary vasculature, after which perfusion was achieved by mounting the heart on a steel cannula. The hearts were perfused retrogradely through the coronary arteries using the Langendorff method. The perfusion fluid was Krebs-Henseleit buffer which consisted (in m*M*) of: NaCl 120, $NaHCO_3$ 20, $CaCl_2$ 1.25, KCl 20, KH_2PO_4 4.63, $MgCl_2$ 1.17, and glucose 8 as substrate. Except for the hypoxia experiments, the buffer was continuously gassed with a mixture of 95% O_2/5% CO_2. The pH of the buffer was 7.4, and the entire system was temperature-controlled at 37°C by water-jacketed chambers and coils. Normal coronary flow rate was maintained at 10 ml/min with a peristaltic pump. Hearts were allowed to contract spontaneously.

Contractile function was determined in terms of apicobasal displacement as previously described (10). A force displacement transducer (Grass FT.03) was connected to the ventricular apex and positioned to yield a diastolic resting tension of 2 g. In addition, a side-arm off the perfusion cannula was connected to a pressure transducer to obtain changes in coronary pressure.

Measurement of tissue energy metabolites

At appropriate periods during the perfusion periods as described in the Results section, hearts were rapidly freeze-clamped between tongs precooled in liquid nitrogen. High-energy phosphates (HEP) and glycogen were extracted in 6% perchloric acid and assayed by standard enzymatic techniques as described in detail previously (10,11).

Experimental protocols

For all experiments, the heart was allowed to equilibrate for 30 min before initiation of any insult protocol. When drugs were examined, they were added 15 min before initiation of the procedures. The following drugs were used: amiloride (174 μ*M*, Sigma Chemical, St. Louis, MO, U.S.A.), 5-(*N*,*N*-hexamethylene) amiloride (HMA, 1 μ*M*, Research Biochemicals, Natick, MA, U.S.A.) and bepridil hydrochloride (10 μ*M*, Sigma). Amiloride and bepridil were dissolved in water (the former only after gentle warming). HMA was dissolved in methanol. Final methanol concentration in the perfusion buffer was 0.0001%, which in itself had no effect on any parameter under study.

To initiate ischemia, perfusion was stopped for 15 min with or without a subsequent 30-min reperfusion period. The oxygen paradox was initiated by replacing oxygenated buffer with one gassed with a mixture of 95% N_2/5% CO_2 for 12 min with or without a further 30-min reoxygenation period. The ischemic and hypoxic durations were selected from initial pilot experiments which identified these periods as resulting in recovery of ~50% in function after either reperfusion or reoxygenation. For production of the calcium paradox, hearts were perfused for 5 min with a calcium-free oxygenated buffer followed by a 30-min calcium repletion reperfusion period. Experiments were also performed to assess the influence of calcium-free perfusion itself on tissue metabolites without a subsequent calcium reperfusion period.

Data analysis

Data were analyzed by analysis of variance (ANOVA) followed by Student-Newman-Keuls test to locate differences between treatment groups. Treatments were considered significantly different at $p < 0.05$.

RESULTS

Myocardial function

Figures 1 and 2 summarize contractile functions in hearts exposed to ischemia/reperfusion or hypoxia/reoxygenation, respectively. Without drug treatment, contractile force recovered to 55 ± 4% of preischemic values when hearts were reperfused for 30 min after 15-min total ischemia. All three drugs significantly enhanced force recovery throughout the reperfusion period. HMA was of particular interest, because with addition of this agent recovery was very rapid, with a 97± 8.1% return to control within 1 min of reflow as compared with 52 ± 6% in control hearts ($p < 0.05$). After 5-min reperfusion, however, this effect was re-

versed to values virtually identical to those achieved with either amiloride or bepridil (Fig. 1).

The effect of hypoxia on cardiac performance was less marked than that observed with ischemia in that there was substantial residual function after 12-min hypoxia (Fig. 2), in contrast to total cessation of contractility after 15-min ischemia. The degree of force decrease in control hearts (26 ± 2.1% of prehypoxia) was significantly blunted by bepridil (42 ± 2.9%), whereas neither amiloride nor HMA exerted any salutary influence. Recovery on reoxygenation was generally better with addition of any of the three agents, although the temporal profile of the beneficial effects varied; e.g., recovery was rapid with addition of HMA (66 ± 4.1 vs. 35 ± 3.2% control after 1 min, $p < 0.05$), in parallel to observations made with ischemia and reperfusion, although this effect decreased to values not significantly different from control after 30-min reoxygenation (Fig. 2). Bepridil treatment resulted in similar rapid recovery of contractility (42 ± 2.9%, $p < 0.05$ from control) that also decreased to values not significantly different from control (control 47 ± 3.1 vs. bepridil 56 ± 4.8%), as was observed with HMA. In contrast to the rapid recovery with HMA and bepridil, the salutary effect of amiloride was delayed, with no beneficial effect until after 15 min of reoxygenation (control 49 ± 5.1 vs. amiloride 71 ± 3.8%, $p < 0.05$).

No significant differences in ventricular rates were noted in either of the two models of injury (Figs. 1 and 2). Thus, recovery in heart rate (HR) was at least 90% in all treatment groups except in hearts perfused with amiloride. Under this condition, recoveries in HR were 79 ± 9.1 and 84.4 ± 8.3% for reperfused and reoxygenated hearts, respectively ($p > 0.05$ from all other groups).

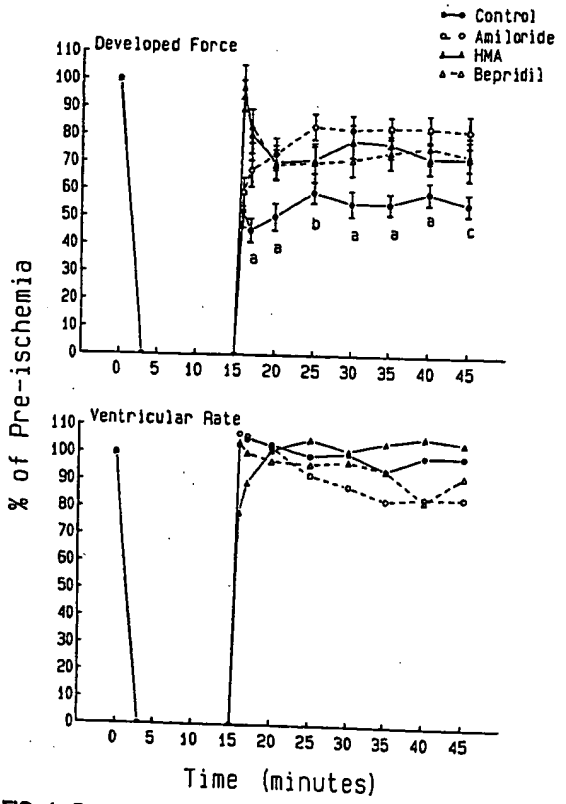

FIG. 1. Response of isolated hearts in terms of developed force and ventricular rate to 15-min ischemia followed by 30-min reperfusion initiated at 0 and 15 min, respectively. Values are mean ± SEM of six experiments except for rate data, for which SE bars have been omitted for clarity. Letters indicate that treatments were statistically significant from control as follows: a, all drug treatments; b, amiloride and 5-(*N*,*N*-hexamethylene) amiloride (HMA) only; c, amiloride and bepridil only. Mean pooled values (±SEM) before initiation of ischemia were 6.7 ± 0.9 g and 342 ± 37 beats/min for developed force and ventricular rate, respectively.

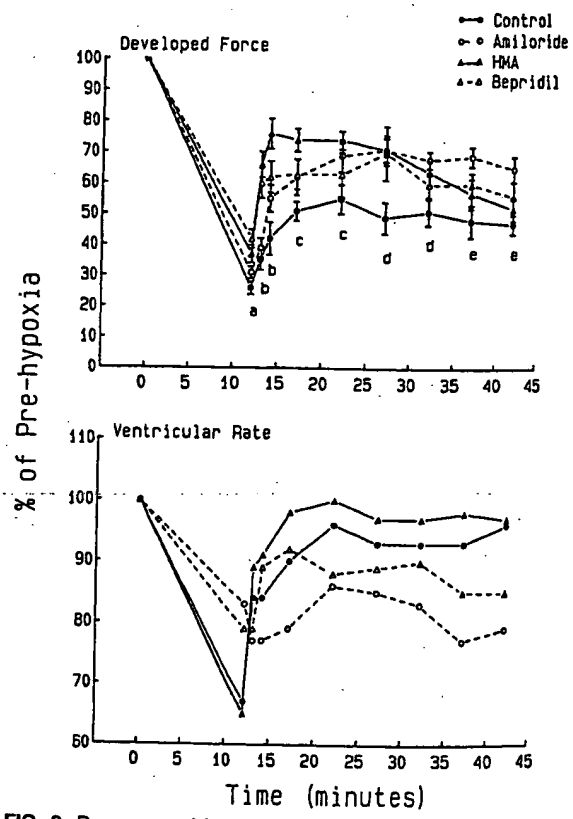

FIG. 2. Response of isolated hearts in terms of developed force and ventricular rate to 12-min hypoxia followed by 30-min reperfusion initiated at 0 and 12 min, respectively. Values are mean ± SEM of six experiments except for rate data, for which SE bars have been omitted for clarity. Different scale is shown for ventricular rate data. Letters indicate that treatments were statistically significant from control as follows: a, bepridil only; b, 5-(*N*,*N*-hexamethylene) amiloride (HMA) and bepridil only; c, HMA only; d, amiloride and HMA only; e, amiloride only. Mean pooled values (±SEM) before initiation of hypoxia were 7.4 ± 1.2 g and 317 ± 34 beats/min for developed force and ventricular rate, respectively.

As shown in Table 1, reperfusion and reoxygenation of untreated hearts produced moderate but not significant increases in resting tension. Although differences were not statistically significant, no increases in resting tension were observed in hearts treated with any of the pharmacologic agents.

Regardless of treatment, no hearts demonstrated any contractile recovery after initiation of the calcium paradox. To obtain some degree of functional assessment, we analyzed resting tension changes during this procedure. As summarized in Table 1, no differences in resting tension between treatment groups were observed.

Effects on HEP and glycogen contents

Table 2 summarizes metabolite changes under various experimental conditions. Diverse effects of the three modes of tissue damage, as well as pharmacologic manipulation, on energy metabolite contents were observed. With regard to ischemia and reperfusion, both HMA and bepridil significantly attenuated the loss in HEP caused by ischemia whereas HMA significantly enhanced CrP repletion on reperfusion. Ischemia produced a substantial decrease in tissue glycogen which was partially restored after reperfusion, a phenomenon unaffected by any of the drugs studied.

In hearts subjected to the oxygen paradox, there was virtually no effect of hypoxia on ATP content whereas CrP was decreased by >60% (Table 2). Thirty-minute reoxygenation returned CrP levels to ~50% of prehypoxic values, an effect significantly enhanced by all three drugs. Hypoxia resulted in a marked decrease in tissue glycogen contents that was partially restored after reperfusion. In posthypoxic reoxygenated myocardium, both amiloride and HMA significantly enhanced glycogen recovery whereas bepridil had no effect.

Calcium-free perfusion had no effect on HEP content, whereas initiation of the paradox by calcium repletion produced a marked (~80%) loss in both ATP and CrP, a phenomenon not affected by either amiloride or HMA (Table 2). However, be-

TABLE 1. *Effect of treatments on resting tension increases in hearts subjected to reperfusion, reoxygenation, and the calcium paradox*

Time (min)	Control	Treatment		
		Amiloride	HMA	Bepridil
Reperfusion				
5	117 ± 8	100 ± 0	100 ± 0	100 ± 0
10	124 ± 8	100 ± 0	100 ± 0	100 ± 0
15	120 ± 7	100 ± 0	100 ± 0	100 ± 0
20	116 ± 5	100 ± 0	100 ± 0	100 ± 0
30	114 ± 7	100 ± 0	100 ± 0	100 ± 0
Reoxygenation				
5	106 ± 7	100 ± 0	100 ± 0	100 ± 0
10	119 ± 6	100 ± 0	100 ± 0	100 ± 0
15	117 ± 8	100 ± 0	100 ± 0	100 ± 0
20	107 ± 6	100 ± 0	100 ± 0	100 ± 0
30	104 ± 8	100 ± 0	100 ± 0	100 ± 0
Ca^{2+} repletion				
5	138 ± 7	146 ± 9	133 ± 7	141 ± 6
10	141 ± 6	147 ± 8	139 ± 9	143 ± 11
15	127 ± 12	131 ± 9	127 ± 6	136 ± 9
20	118 ± 7	121 ± 5	118 ± 10	123 ± 8
30	118 ± 9	116 ± 7	115 ± 8	120 ± 10

HMA, 5-(*N*,*N*-hexamethylene) amiloride.
Values are mean ± SEM (n = 6) and indicate percentage of control. Time indicates minutes after reperfusion, reoxygenation, or Ca^{2+} repletion.

TABLE 2. *Changes in tissue high-energy phosphates and glycogen contents with various treatments with or without drugs*

Treatment	Metabolite		
	ATP	CrP	Glycogen
15-min ischemia			
Control	20 ± 2.5	7.4 ± 1.6	24 ± 5
Amiloride	23 ± 1.7	12.3 ± 4.1	30 ± 7
HMA	36 ± 4[a]	23.8 ± 5.7[a]	29 ± 6
Bepridil	39 ± 4[a]	30.4 ± 4.1[a]	34 ± 8
1-min reperfusion			
Control	57.5 ± 6.3	40 ± 5.8	57 ± 4
Amiloride	62.5 ± 5.0	28 ± 5.0	66 ± 7
HMA	55 ± 8.8	29 ± 4.1	60 ± 4
Bepridil	59 ± 5.0	31 ± 6.0	58 ± 8
30-min reperfusion			
Control	81 ± 5	49 ± 7	71 ± 13
Amiloride	80 ± 8.8	38 ± 6	69 ± 12
HMA	105 ± 8.0	67 ± 4	70 ± 6
Bepridil	89 ± 10	56 ± 9	69 ± 11
12-min hypoxia			
Control	87 ± 6	33 ± 2	37 ± 9
Amiloride	85 ± 5	27 ± 4.1	60 ± 7
HMA	81 ± 6	24 ± 2	34 ± 10
Bepridil	79 ± 8	24 ± 3	32 ± 4
1-min reoxygenation			
Control	95 ± 5	45 ± 3	25 ± 3
Amiloride	89 ± 8	48 ± 4	30 ± 6
HMA	87 ± 7	47 ± 4	41 ± 4[a]
Bepridil	83 ± 6	51 ± 5	35 ± 4
30-min reoxygenation			
Control	99 ± 6	49 ± 3	59 ± 6
Amiloride	97 ± 8	62 ± 4	88 ± 5[a]
HMA	93 ± 7	64 ± 4	76 ± 5[a]
Bepridil	97 ± 7	67 ± 4	34 ± 8[a]
5-min Ca^{2+}-free			
Control	100 ± 3	125 ± 6	162 ± 13
Amiloride	115 ± 7	117 ± 8	130 ± 29
HMA	122 ± 14	97 ± 6	149 ± 15
Bepridil	114 ± 7	150 ± 15	270 ± 33[a]
1-min Ca^{2+} repletion			
Control	20 ± 0.4	19 ± 1.8	127 ± 11
Amiloride	27 ± 1.1	20 ± 3	116 ± 19
HMA	25 ± 4	24 ± 1.9	101 ± 16
Bepridil	56 ± 7[a]	39 ± 4.7[a]	112 ± 9
30-min Ca^{2+} repletion			
Control	14 ± 1.2	7.2 ± 0.9	50 ± 7
Amiloride	8.3 ± 0.7	8.2 ± 0.5	67 ± 6
HMA	16.8 ± 5.1	8.8 ± 0.7	70 ± 8
Bepridil	8.5 ± 1.9	20 ± 4.3	61 ± 9

HMA, 5-(*N*,*N*-hexamethylene) amiloride.
Values are mean ± SE (n = 5–7) and indicate percentage of change from either preischemia, pre-Ca^{2+}-free or prehypoxia.
[a] $p < 0.05$ from control.

pridil significantly enhanced HEP content in hearts subjected to 1-min calcium repletion as well as CrP content after 30-min calcium reperfusion. Calcium-free perfusion increased glycogen to 162 ± 13% of control values, an effect significantly enhanced by bepridil (270 ± 33% of control).

DISCUSSION

Stimulation of Na^+/H^+ exchange activity on reperfusion of ischemic myocardium has been suggested as a potential contributing factor toward injury observed with reflow (4) because activation of the exchanger would result in increased Na^+ influx followed by increases in intracellular calcium levels through Na^+/Ca^{2+} exchange. Support of this hypothesis stems from studies showing that amiloride, a nonspecific Na^+/H^+ exchange inhibitor, protects against myocardial reperfusion injury in terms of improved functional recovery, reduction in the incidence of arrhythmias, preservation of ultrastructure, and inhibition of enzyme release (3,12,13). Moreover, the protection afforded by amiloride has been shown to be associated with concomitant attenuation of tissue sodium and calcium accumulation during early reperfusion, thus offering support for an important role of Na^+/Ca^{2+} exchange (13).

The present study was performed to address four primary questions. First, can the protective effect of amiloride be mimicked by HMA, a markedly more potent and specific Na^+/H^+ exchange inhibitor (14)? Second, can the protection afforded by these drugs also be observed using two other models of reperfusion injury, i.e., the oxygen and calcium paradoxes? Third, can protection also be provided by bepridil, a nonspecific inhibitor of the Na^+/Ca^{2+} exchanger? Last, can any protective effect in terms of function be related to improved myocardial energy metabolic status?

Our results clearly show that all pharmacologic manipulations improved functional recovery in postischemic reperfused myocardium, although the temporal profiles of return of function were different. The protective effects of amiloride and HMA support the concept of Na^+/H^+ exchange activation as a contributing factor to reperfusion injury. Moreover, protection was also observed in reoxygenated hearts primarily during early reoxygenation. HMA and bepridil were particularly effective in this regard, producing rapid restoration of contractility after only 1-min reoxygenation. However, the protective effect of both compounds reversed with continued perfusion, although the mechanism underlying this phenomenon is unknown. Amiloride was the most consistent protective agent against both reperfusion and reoxygenation injury. This may reflect the nonspecificity of amiloride; e.g., this drug can also inhibit various myocardial enzymes as well as Na^+/Ca^{2+} exchange (15), properties that may result in added salutary actions. Moreover, amiloride has been shown to prevent an increase in intracellular calcium in ischemic nonreperfused myocardium, a salutary effect most likely unrelated to inhibition of Na^+/H^+ exchange activation (16). Despite some variability in terms of contractile recovery after reperfusion or reoxygenation, complete prevention of resting tension increase is further evidence for a protective action of these drugs in both models of injury. Together, these results suggest the likelihood that Na^+/H^+ exchange activation occurs in reoxygenated myocardium and contributes to contractile dysfunction. In addition, the protective effect of bepridil suggests Na^+/Ca^{2+} exchange as a contributing factor to injury, in agreement with previous results, at least with regard to reoxygenation (17). Surprisingly, Crake and Poole-Wilson (17) using rabbit intraventricular septum, failed to demonstrate protection with amiloride, a discrepancy that may be related to the experimental model.

Not surprisingly, our results showed different metabolic changes in ischemic and hypoxic hearts, with the former resulting in a substantially greater loss in both HEPs (as well as glycogen) whereas hypoxia-induced loss in HEP occurred primarily at the expense of CrP. Because the durations of ischemia and hypoxia were selected to result in ~50% recovery in function, the results suggest that these metabolic changes were unlikely to influence functional recovery when ischemia or hypoxia is brief, a finding in agreement with results of other studies showing a dissociation between HEP contents at the end of ischemia and postreperfusion recovery of function (18–20). Although the degree of ATP depletion may be of importance to functional recovery, this may be true only when ATP contents reach critically low levels (20). The dissociation between energy status and functional recovery is also supported by the dissimilar effects of drugs on energy metabolites as compared with their reasonably consistent influence on contractile recovery. Indeed, analysis by linear regression analysis showed no significant relation between any metabolite and either postreperfusion or posthypoxic contractile recovery (data not shown).

None of the drugs examined improved contractile recovery in hearts subjected to the calcium paradox. There are two possible explanations for this lack of effect. First, the calcium paradox produces extensive cell disruption on reintroduction of calcium, substantially greater than that which occurs with reperfusion or reoxygenation injury (8,21). The complete lack of contractility concomitant with resting tension increases observed in the present study supports this contention and suggests that the degree of injury was sufficient to be resistant to pharmacologic interventions. Second, an initial acid

load such as that observed during ischemia or hypoxia predisposes the heart to Na^+/H^+ exchange activation on reintroduction of flow or oxygen and thus should be considered a prerequisite for Na^+/H^+ exchange involvement in reperfusion or reoxygenation injury. In this regard, calcium-free perfusion of isolated rat hearts was shown not to affect intracellular pH, thus precluding any stimulus for Na^+/H^+ exchange activation (22). Although controversy exists regarding the role of intracellular sodium in mediating the calcium paradox (23), Na^+ entry during calcium-free perfusion has been proposed to result in rapid activation of Na^+/Ca^{2+} exchange when calcium is reintroduced (24,25). Thus, the failure of bepridil to offer substantive protection against the calcium paradox was surprising, but again may reflect the severe nature of the calcium paradox-induced injury.

The metabolic profiles with regard to HEP observed in the calcium paradox agree with observations reported by other investigators (26). Thus, calcium-free perfusion results in little change in either ATP or CrP contents, whereas reintroduction of calcium produces rapid and severe loss of both compounds. The early attenuation of HEP depletion by bepridil is suggestive of early Na^+/Ca^{2+} exchange activation on reintroduction of calcium. A surprising observation was the increase in tissue glycogen content after 5-min calcium-free perfusion, particularly with addition of bepridil. The mechanism for this effect is uncertain, but may involve diminished calcium entry, resulting in depressed calcium-activated glycogenolysis.

Our study has several limitations. First, a pharmacologic approach was used to probe the involvement of ion exchangers in mediating cardiac injury and direct measurement of ion transport was not possible with our model. Nonetheless, the ability of amiloride and especially of HMA to protect against reperfusion and reoxygenation injury further supports the Na^+/H^+ exchange hypothesis. The results with bepridil should be interpreted with caution because despite exhibiting potent Na^+/Ca^{2+} exchange-inhibiting properties the drug also inhibits various other cellular processes, including voltage-dependent Ca^{2+} channels and ATPases as well as mitochondrial functions (9). Unfortunately, no pharmacologic agents that selectively inhibit Na^+/Ca^{2+} exchange without having modulatory effects on other aspects of cellular homeostasis are currently available. Nonetheless, we speculate, based on the amiloride and HMA data, that the protective effect of bepridil in the reperfused and reoxygenated heart was mediated by inhibition of Na^+/Ca^{2+} exchange, which in turn was initially stimulated by enhanced Na^+/H^+ exchange activity. Therefore, inhibition of the latter probably represents a potentially useful approach toward improvement of post-reperfusion myocardial contractile function.

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